REMARKS

Novelty Rejection under 35 U.S.C. 102(f):

Claims 1, 19-20, 22-27, and 32 are rejected under 35 U.S.C. 102(f) over Boger et al., *J. Org. Chem.* (2001) **66**, 2207-2216 (Boger I) on the basis that the named inventor of the present application did not himself invent the claimed subject matter. More particularly, the Examiner asks that applicant show evidence of being the first to utilize bromine for the "**X**" variable in the instant claims in view of Scheme 1 of Boger I. Applicant traverses this basis for rejection.

Firstly, this basis for rejection is inapplicable to claims 20, 26, 27, and 32 because these claims utilize iodine for the "**X**" variable and not bromine.

Secondly, support for claims 1, 19-20, 22-27, and 32 and the use of a **halide** for the "**X**" variable is found in the Specification as follows:

> "An aryl **halide** is alkylated with 1,3-dichloropropene and a catalytic amount of **n**-tetrabutylammonium iodide for forming a vinyl chloride." Specification, page 2, lines 24-26.

The use of an aryl halide, as disclosed in the specification, includes the use of an aryl bromide.

Further support for claims 1, 19-20, 22-27, and 32 and the use of a bromide for the "**X**" variable is found in Figure 3 of the present application. Note the use of the aryl bromide in Figure 3 as a key intermediate for a subsequent cyclization step, as covered by claims 1, 19, and 22-25.

Thirdly, Boger I admits that it did not originate the idea of the use of aryl bromide as a key intermediate for a subsequent cyclization step. A description and explanation of Scheme 1 is provided in Boger I within the last paragraph of page 2208 second column and continuing on through first paragraph of page 2209. Within this description, Boger I indicates that the original teaching that aryl bromide (**10**) (of Boger I) is a key intermediate for the subsequent cyclization step was disclosed in references **22**, viz., 1.) Patel, et al, *J. Org Chem* (1997) **62**, 8868; and 2.) Boger et al., *Tetrahedron Lett.* (1998) **39** 2227 (referred herein as Boger II). Copies of both references are attached. Please note that Scheme 2 of Boger II is identical to Figure 3 of the present application. Indeed, the present application was based, in part, on Boger II.

Fourthly, the priority date of the present application, viz., December 8, 1997, predates the publication date of Boger I, viz., March 13, 2001. Please note that the priority date of the present application also predates the publication date of Boger II (April 16, 1998) and of Patel (Dec 12, 1997).

Withdrawal of this basis of rejection is respectfully requested.

Novelty Rejection under 35 U.S.C. 102(g):

Claims 1, 19-20, 22-27, and 32 are further rejected under 35 U.S.C. 102(g) over U.S. Patent No. 6,534,660 (Yongxin et al., amended by certificate of correction on July 29, 2003 as "Zhao et al.") on the basis that the named inventor of the present application was not the first to invent the claimed subject matter. Applicant traverses this basis for invention.

The Examiner has failed to present any evidence regarding the date of conception and reduction to practice by Zhao et al. Applicant notes that Applicant's priority date is 5 years and 4 months senior to Zhao. Applicant requests that this basis for rejection be withdrawn for lack of supporting evidence.

Interference:

Applicant notes substantial overlap between claim 1 of the present application and claim 1 of Zhao et al. If Examiner believes that there is an interference between the two claims, a declaration of interference is requested.

Summary:

Applicant has established under 35 U.S.C. 102(f) that the named inventor of the present application is the earlier inventor of Claims 1, 19-20, 22-27, and 32 as compared to Boger I (Boger et al., *J. Org. Chem.* (2001) **66**, 2207-2216).

Applicant has also established under 35 U.S.C. 102(g) that the Examiner has failed to establish a *prima facie* case that the invention of Claims 1, 19-20, 22-27, and 32 of the present application was made subsequent to the Zhao et al.

Allowance of claims 1, 19-20, 22-27, and 32 is respectfully requested. If any of the claims of Zhao et al. are deemed by the Examiner to interfere with claims 1, 19-20, 22-27, and 32 of the present application, a declaration of interference is also requested.

Respectfully submitted,

July 15, 2004
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Tetrahedron Letters 39 (1998) 2227–2230

TETRAHEDRON LETTERS

Synthesis of CC-1065 and Duocarmycin Analogs via Intramolecular Aryl Radical Cyclization of a Tethered Vinyl Chloride

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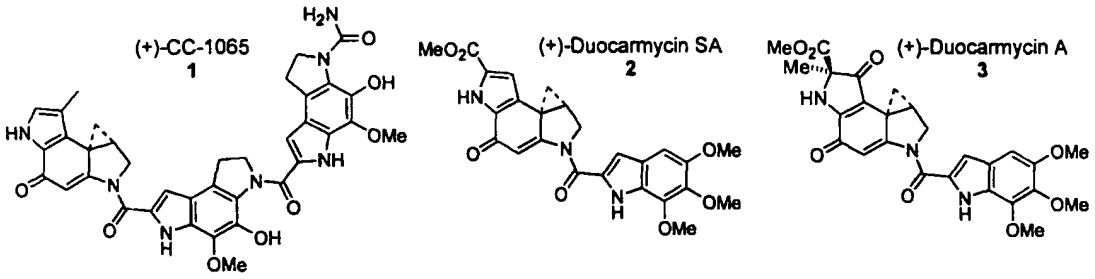
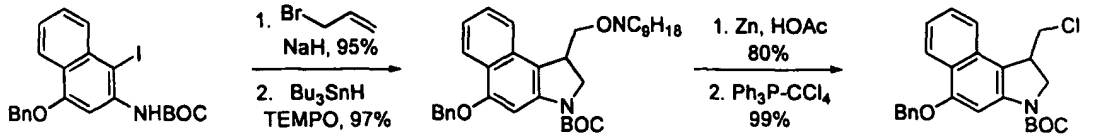
Abstract: The 5-*exo-trig* radical cyclization of an aryl halide onto a tethered vinyl chloride produces the 3-chloromethyl dihydroindole precursors for CC-1065 and duocarmycin analogs with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization. The generality of this approach was examined in the context of six CC-1065 and duocarmycin analogs previously synthesized in this laboratory.

CC-1065 (**1**)[1] and the duocarmycins **2**[2] and **3**[3,4] are the parent members of a class of potent antitumor antibiotics that derive their biological properties through sequence selective alkylation of DNA.[5] DNA alkylation occurs through a common structural feature found in the natural products, a cyclopropatetrahydropyrroloindolone in which nucleophilic attack by adenine takes place at the least substituted carbon of the activated cyclopropane. Synthetic efforts[6] which have focused both on the natural products and on functional analogs containing deep-seated structural modifications have served to define many of the fundamental principles underlying the relationships between structure, chemical reactivity and biological properties within this family, and have advanced the understanding of the origin of the sequence selectivity[5,7] and catalysis[7,8] of the DNA alkylation reaction by **1–3**.



Central to our synthesis of CC-1065[9] and its extension to a number of analogs[6] was the evolution[10,11] and ultimate development[12] of a 5-*exo-trig* radical cyclization followed by an *in situ* primary radical trap with TEMPO[13] as depicted for CBI (Scheme 1). While this method has proved versatile, Patel and co-workers have recently described a more concise route in the synthesis of a benzofuran analog of **2** which further improves on this approach and utilizes a novel intramolecular 5-*exo-trig* radical cyclization onto a tethered vinyl chloride (Scheme 2).[14]

Scheme 1



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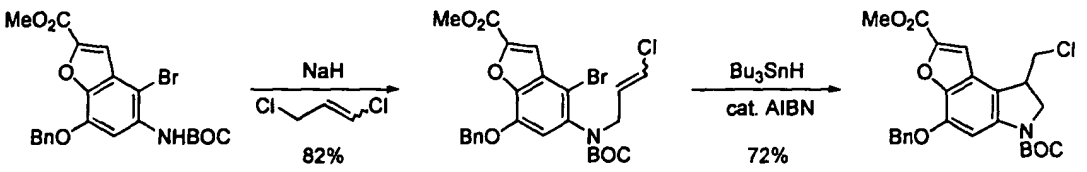
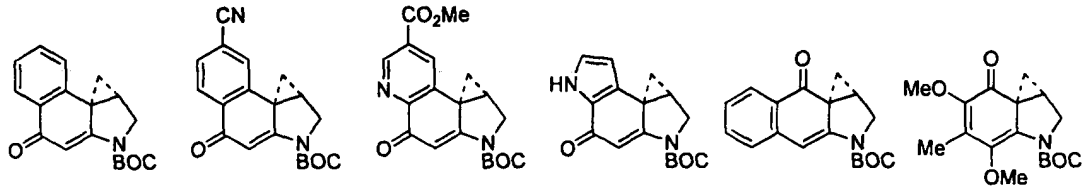
PII: S0040-4039(98)00232-9

Scheme 2



This represents a significant synthetic improvement, shortening the reaction sequence from four steps to two steps and directly provides the 3-chloromethyl dihydroindoles set up for deprotection and subsequent spirocyclization.

In the course of our own ongoing efforts, we have had the occasion to examine and implement this cyclization in the synthesis of a number of previously disclosed as well as new alkylation subunit analogs which serves to establish the generality of this approach. Thus, the C-ring construction for CBI (**4**),[10,12] CCBI (**5**),[15] CPyI (**6**), desmethyl-CPI (**7**), *iso*-CBI (**8**),[16] and a mitomycin-hybrid (**9**) have been investigated. *N*-alkylation of the appropriately functionalized aryl halides **10a–g**, which were obtained through electrophilic halogenation (entries 1–5) or directed ortho metallation (entries 6 and 7), with 1,3-dichloropropene provided the radical cyclization precursors **11a–g** in high yields. Treatment with Bu_3SnH and a catalytic amount of AIBN[13] in benzene or toluene (60–90 °C) cleanly effected 5-*exo-trig* radical cyclization to form the 3-chloromethyl dihydroindoles (**12a–g**, Table 1).



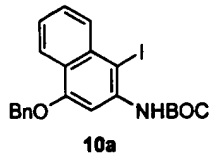
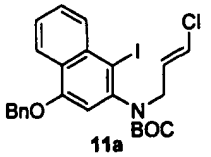
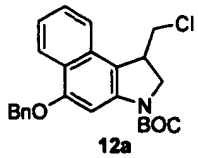
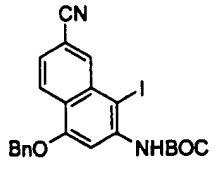
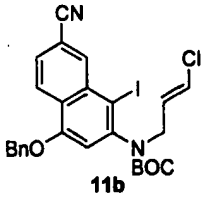
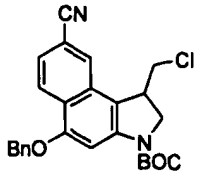
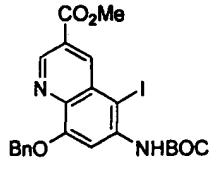
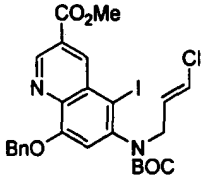
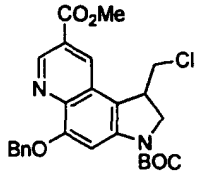
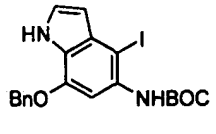
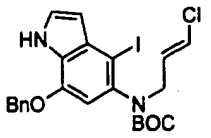
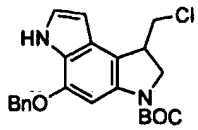
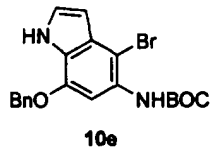
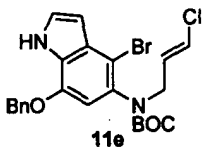
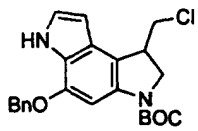
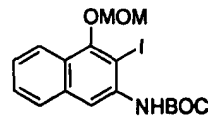
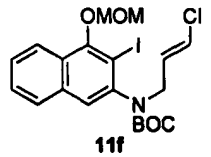
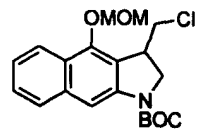
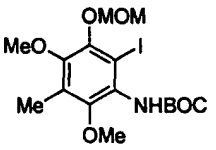
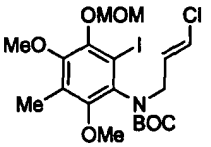
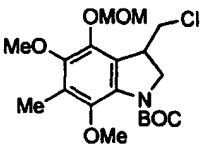
CBI	CCBI	CPyI	desmethyl-CPI	*iso*-CBI	mitomycin hybrid
4	**5**	**6**	**7**	**8**	**9**

This two-step transformation was found to work well with benzene, naphthalene, indole and quinoline derivatives, with aryl iodides as well as aryl bromides (see entries 4 and 5), with little to no effect in the consistently high yields for both steps. Minor optimization efforts revealed that higher yields may sometimes be obtained with addition of *n*-Bu_4NI to the alkylation reaction, as well as the use of toluene versus benzene and higher reaction temperatures for the free radical cyclization. It was observed, as was noted by Patel,[14] that deoxygenation of the solvent prior to radical cyclization enhanced both the rate and yield of the reaction.

In summary, this useful intramolecular aryl radical cyclization onto a vinyl chloride, as introduced by Patel,[14] was successfully applied to the C-ring synthesis of six CC-1065 and duocarmycin analogs. This concise approach has effectively shortened the synthesis of each by two steps and suggests that this approach to the cyclopropatetrahydropyrroloindolones and analogs will be utilized extensively in future efforts on this important class of agents.[17]

Acknowledgments. We gratefully acknowledge the financial support of the National Institute of Heatlh (CA55276) and the award of an ACS Organic Division Fellowship (RMG) sponsored by Zeneca Pharmaceuticals.

Table 1. Two-step Synthesis of 3-Chloromethylindolines

Entry	Aniline (10)	Conditions	Product (11)	Yield	Conditions	Indoline (12)	Yield
1	 **10a**	a	 **11a**	98%	c	 **12a**	90%
2	 **10b**	a	 **11b**	88%	c	 **12b**	85%
3	 **10c**	a	 **11c**	94%	c	 **12c**	82%
4	 **10d**	a	 **11d**	70%	d	 **12d**	72%
5	 **10e**	a	 **11e**	49%	d	 **12e**	77%
6	 **10f**	b	 **11f**	96%	c	 **12f**	96%
7	 **10g**	b	 **11g**	96%	c	 **12g**	96%

[a] NaH, 1,3-dichloropropene, DMF, 25 °C; [b] NaH, 1,3-dichloropropene, nBu$_4$NI, DMF, 25 °C; [c] AIBN (cat.), Bu$_3$SnH, benzene, 60-75 °C; [d] AIBN (cat.), Bu$_3$SnH, toluene, 90 °C.

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11. For a review of the evolution of a free radical cyclization approach to CC-1065/duocarmycins and their analogs, see: Boger, D. L. *Israel J. Chem.* **1997**, *37*, 119.
12. Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271.
13. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical; AIBN = 2,2'-azobisisobutyronitrile
14. Patel, V. F.; Andis, S. L.; Enkema, J. K.; Johnson, D. A.; Kennedy, J. H.; Mohamadi, F.; Schultz, R. M.; Soose, D. J.; Spees, M. M. *J. Org. Chem.* **1997**, *62*, 8868.
15. Boger, D. L.; Han, N.; Tarby, C. M.; Boyce, C. W.; Cai, H.; Jing. Q.; Kitos, P. A. *J. Org. Chem.* **1996**, *61*, 4894.
16. Boger, D. L.; Garbaccio, R. M.; Jing, Q. *J. Org. Chem.* **1997**, *62*, 8875.
17. *Experimental Procedure Exemplified with 5-(Benzyloxy)-3-(tert-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3H-benz[e]indole* (**12a**): Sodium hydride (60% in oil, 125 mg, 3.00 mmol) was added to a stirred solution of **10a** (500 mg, 1.05 mmol) in anhydrous DMF (30 mL) at 0 °C. The resulting suspension was warmed to 25 °C over 15 min, and neat 1,3-dichloropropene (275 μL, 3.00 mmol) was added. The mixture was stirred for 1 h at 25 °C before the solution was poured into water (100 mL), and extracted with EtOAc (2 × 50 mL). Chromatography (SiO_2, 2.5 × 15 cm, 10% EtOAc/hexane) gave pure **11a** as a yellow oil (565 mg, 98%). A solution of **11a** (550 mg, 1.00 mmol) in 60 mL anhydrous benzene under N_2 was treated with Bu_3SnH (324 μL, 1.22 mmol) and AIBN (10 mg, 0.07 mmol). After degassing for 15 min with a stream of N_2, the solution was warmed at 80 °C for 1 h. Evaporation of the solvent under reduced pressure and recrystallization of the residue from hexanes gave pure **12a** (300 mg, 71%). Purification of the remaining mother liquor by flash chromatography (SiO_2, 2.5 × 15 cm, 10% EtOAc/hexane) gave a further 81 mg of **12a**, providing a total yield of 381 mg (90%).

Tetrahedron Letters

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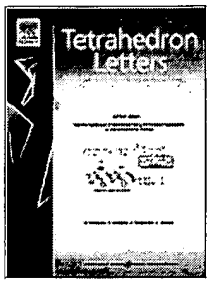

1. **Synthetic studies toward diazonamide A. Preparation of the benzofuranone-indolyloxazole fragment** • **ARTICLE**
Pages 2223-2226
Peter Wipf and Fumiaki Yokokawa
Abstract | Abstract + References | PDF (266 K)

2. **Synthesis of CC-1065 and duocarmycin analogs via intramolecular aryl radical cyclization of a tethered vinyl chloride** • **ARTICLE**
Pages 2227-2230
Dale L. Boger, Christopher W. Boyce, Robert M. Garbaccio and Mark Searcey
Abstract | Abstract + References | PDF (294 K)

3. **Expanded cyclophanes 1. Synthesis and structure of 4,17-dithia[7.7]metacyclophane-1,6,14,19-tetrayne** • **ARTICLE**
Pages 2231-2234
Graham J. Bodwell, Tom J. Houghton and David Miller
Abstract | Abstract + References | PDF (325 K)

4. **Solution phase synthesis of a spiro[pyrrolidine-2,3'-oxindole] library via a three component 1,3-dipolar cycloaddition reaction** • **ARTICLE**
Pages 2235-2238
Demosthenes Fokas, William J. Ryan, David S. Casebier and David L. Coffen
Abstract | Abstract + References | PDF (311 K)

5. **Stereoselective syntheses of the rhizoxin C(1)C–(9) and C(12)–C(26) subunits** • **ARTICLE**
Pages 2239-2242
Steven D. Burke, Jian Hong and Andrew P. Mongin
Abstract | Abstract + References | PDF (324 K)

6. **Equisetin and a novel opposite stereochemical homolog phomasetin, two fungal metabolites as inhibitors of HIV-1 integrase** • **ARTICLE**
Pages 2243-2246

Total Synthesis of Seco (+)- and *ent*-(−)-Oxaduocarmycin SA: Construction of the (Chloromethyl)indoline Alkylating Subunit by a Novel Intramolecular Aryl Radical Cyclization onto a Vinyl Chloride

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A practical, total synthesis of seco-(+)-oxaduocarmycin **3a**, an analogue of the highly cytotoxic natural product, duocarmycin SA (**1**), is described. The 13-step synthesis features a novel and efficient intramolecular aryl radical cyclization onto a vinyl chloride as a direct entry to the (chloromethyl)indoline alkylating subunit **14**. Subsequent resolution, utilizing a preparative Chiralpak AD column, provided enantiomerically pure alkylating subunits **14a** and **14b** which were elaborated to seco-(+) and *ent*-(−)-oxaduocarmycins, **3a** and **3b**, respectively. The natural enantiomer **3a** was active at pM concentrations and exhibited 7−50-fold higher potentcy than its enantiomer **3b** in *in vitro* cytotoxicity assays.

Introduction

(+)-Duocarmycin SA (**1**),[2] isolated from *Streptomyces sp.* DO113, is the newest member of a class of potent antitumor antibiotics[3,4] that are structurally and biologically related to (+)-CC-1065 (**2**).[5] In common, these natural products possess a cyclopropanoindolinone linked to a DNA binding subunit as the pharmacophore responsible for the sequence-selective minor groove alkylation of duplex DNA[5] and the exceptionally potent cytotoxic activity.[5,6] Detailed studies, however, reveal two critical features that distinguish (+)-duocarmycin SA (**1**) in its interaction with duplex DNA and suggest that it may represent the most exciting agent in the series.[7,8] The first feature relates to the extent of the noncovalent DNA binding[8] which stabilizes the *reversible*[9] alkylation of DNA while providing (+)-duocarmycin SA (**1**) with the full biological properties of the irreversible alkylating agent, (+)-CC-1065 (**2**).[10] This, in combination with the implications that the extent of the noncovalent stabilization may be related to the delayed, fatal hepatotoxicity associated with (+)-CC-1065 (**2**),[9a,10] suggests that (+)-duocarmycin SA (**1**) may prove to be a better therapeutic agent. Second, as the most stable natural product in this class of agents,[11] (+)-duocarmycin SA[12] (**1**) is also the most potent,[6a] a finding that is consistent with a correlation between solvolytic stability and cytotoxic potency that was established within a series of agents possessing sufficient reactivity to alkylate DNA.[13] Together, these characteristics provide rationale for the development of (+)-duocarmycin SA (**1**) and related agents as potent oncolytics for the treatment of human cancers.[14]

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(12) The name duocarmycin SA originates from duocarmycin stable A.

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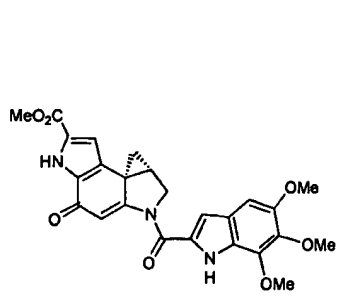
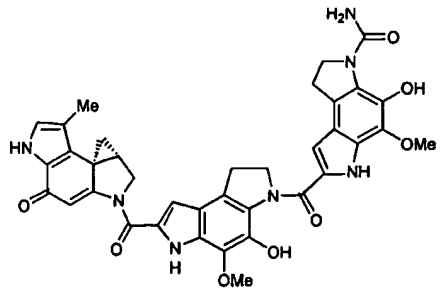
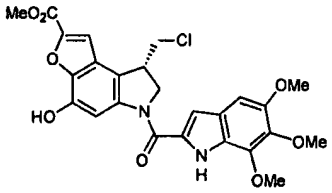
Chart 1



1: (+)-Duocarmycin SA



2: (+)-CC-1065

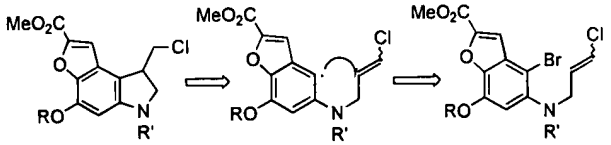


3a: *seco*-(+)-Oxa-Duocarmycin SA

Seco-(+)-oxaduocarmycin SA **3a** (LY307918) is an analogue in which the fused pyrrole ring in the alkylating subunit of **1** is replaced with a potentially metabolically more inert furan ring,[15] and the cyclopropanoindolinone pharmacophore is masked as a (chloromethyl)hydroxyindoline, a prodrug form which is known to demonstrate indistinguishable biological properties from its active form.[16] The unexpected observation that both (+)-**1** and its enantiomer *ent*-(−)-**1** alkylate DNA with comparable efficiency,[17] prompted us to evaluate both (+)-**3a** and *ent*-(−)-**3b** as potentially useful oncolytics. A practical synthetic route was, therefore, required to provide sufficient quantities of both the enantiomers for a full evaluation of their biological properties.

Herein, we report an efficient and practical total synthesis of (+)-**3a** and *ent*-(−)-**3b** in which the key transformation involves a C−C bond formation via a *novel 5-exo-trig cyclization of an aryl radical onto a vinyl chloride*[18] to provide a direct entry into the (chloromethyl)indoline ring system (Scheme 1).[19] Subsequent resolution, by chromatographic separation on a chiral column, leads to enantiomerically pure alkylating subunits, which are then elaborated to furnish both enantiomers of seco-oxaduocarmycin SA (**3**).[20]

Scheme 1



Results and Discussion

Alkylation of the potassium salt of commercially available hydroxybenzaldehyde **4** with ethyl bromoacetate cleanly provided **5**[21] (Scheme 2). Intramolecular aldol cyclization of **5** followed by dehydration was most effectively achieved in one step with DBU in refluxing ethanol to directly give benzofuran **6**[21] in a modest 44% yield. O-Demethylation, with concomitant ester hydrolysis, occurred on heating **6** with excess, neat pyridine hydrochloride[22] at 170 °C to give hydroxy acid **7**, which was directly reesterified with acidic methanol to give the desired methyl ester **8** in an 95% overall yield. Reduction

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(16) Seco-(+)-duocarmycin SA exhibits cytotoxic activity as well as a DNA alkylating selectivity and efficiency identical with those of (+)-duocarmycin SA: see ref 8a.

(17) *ent*-(−)-Duocarmycin SA alkylates DNA but only at concentrations approximately 10× that required for (+)-duocarmycin SA. Consequently, the natural enantiomer is 10× more effective than the unnatural enantiomer: see ref 5e.

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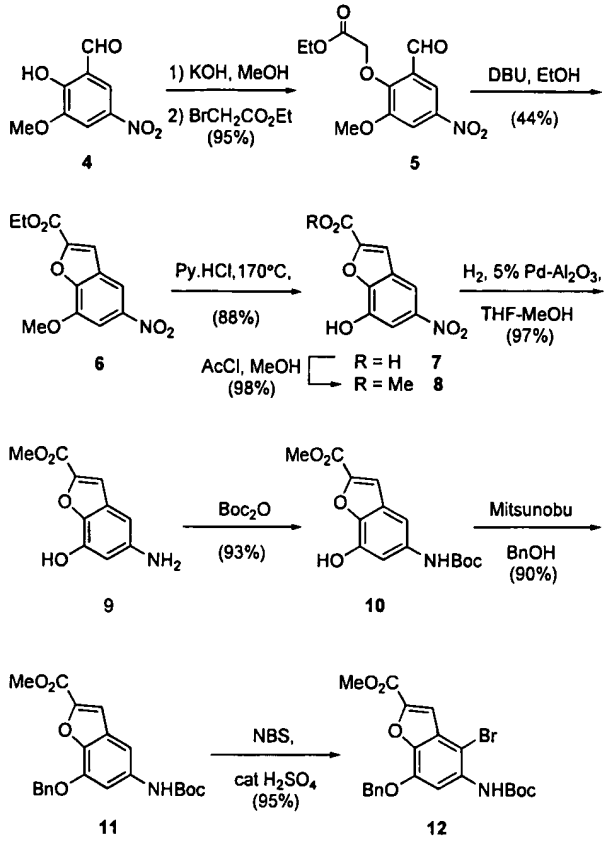
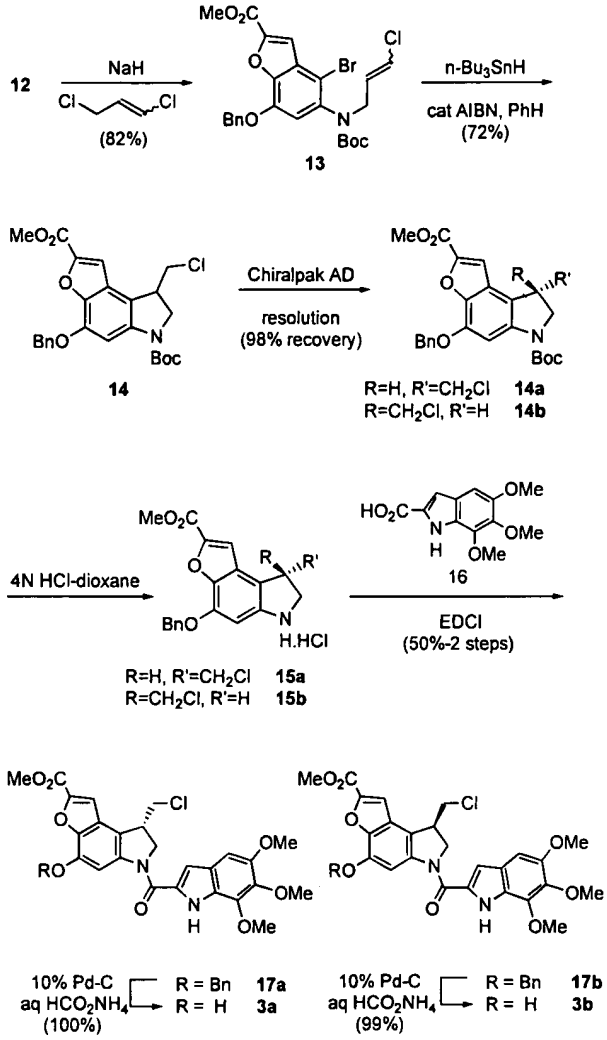
Scheme 2



of the nitro group in **8**, using H_2 over 5% Pd–Al_2O_3 in a solvent mixture of THF:MeOH, followed by protection of the resulting amine **9**, led to Boc aniline **10**. O-Benzylation of phenol **10**, effected under standard Mitsunobu[23] conditions, then gave fully protected benzofuran **11**. A low-temperature, electrophilic aromatic bromination of **11**, using NBS in the presence of catalytic concentrated H_2SO_4,[24] led to regiospecific introduction of the C-4 bromide to provide **12** as the sole product in an excellent yield. Deprotonation of amide **12**, using NaH, followed by alkylation[24] of the resulting anion with commercially available (*E*:*Z*)-1,3-dichloropropene gave an inconsequential mixture of *E*:*Z* isomers of vinyl chloride **13**, the desired precursor for the key aryl radical cyclization (Scheme 3). A deoxygenated solution of aryl bromide **13** in 0.015 M benzene was heated at reflux for 3.5 h in the presence of 1.1 equiv of tri-*n*-butyltin hydride and cat. AIBN to give the desired, fully functionalized alkylating subunit **14** in 72% yield.[25] Particularly noteworthy was the simple workup employed that involved trituation in hexanes followed by filtration to provide pure **14** as a white solid with no detectable levels of tin residues. The cyclized product **14** is formed in a highly chemoselective manner believed to proceed *via* an initial, preferential homolysis of the weaker aryl C–Br bond[26] in **13** to generate an aryl radical which undergoes a preferred

Scheme 3



5-exo-trig intramolecular cyclization[27] onto the proximal vinyl chloride acceptor. A hydrogen radical quench of the resulting (chloromethyl)indoline radical terminates the chain reaction. The absence of a methylindoline product that could originate from reduction of **14** indicates that the chloromethyl functionality was, indeed, stable to homolysis under these reaction conditions.

Resolution,[28] on a preparatively useful scale was readily accomplished by direct chromatographic separation of racemate **14** on a preparative Chiralpak AD (Amylose)[29] column (8 cm × 24 cm, n-PrOH:hexane (51:49), column volume (CV) = 964 mL, 225 mL/min flow rate), to provide multigram quantities (360 mg in 300 mL eluent/injection) of enantiomers (+)-**14a** (t_R = 5.6 min, 97.6 % ee, 49 % recovery) and *ent*-(−)-**14b** (t_R = 7.4 min, 95.55 % ee, 48 % recovery). Acid-mediated deprotection

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(24) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321.
(25) A minor uncyclized product (<2%), resulting from reduction of the aryl bromide, was detected by ^{1}H NMR but not isolated.
(26) An example of regiospecific homolysis of a C–Br bond in the presence of a C–Cl bond has been reported: Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3721.
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(28) The amine, derived from deprotection of **14**, proved unstable and was unamenable to resolution through classical fractional recrystallization of diastereomeric salts. Covalent diastereomers, prepared by attachment of chiral agents to either the amine or phenol derivatives of **14**, were not readily separable by chromatograhic means.
(29) Effective separations on related agents have been previously achieved by direct chromatographic resolution on a ChiraCel OD column: (a) Boger, D. L.; Yu, W. *J. Am. Chem. Soc.* **1994**, *116*, 7996. (b) Boger, D. L.; Bollinger, B.; Johnson, D. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2207. (c) Boger, D. L. et al, *J. Am. Chem. Soc.* **1997**, *119*, 4977. See also ref 8a.

Table 1. *In Vitro* Cytotoxicity, IC_{50} (nM)

	tumor cell line		
	T222	CCRF-CEM	GC3/C1
(+)-**3a**	0.39	0.23	0.10
ent-(−)-**3b**	19.4	1.59	0.70

of (+)-**14a** and *ent*-(−)-**14b** selectively removed the Boc group to give unstable amine salts (+)-**15a** and *ent*-(−)-**15b**, which were directly coupled with 5,6,7-trimethoxyindole-2-carboxylic acid[6a] **16**, under standard EDCI-promoted coupling conditions,[30] to furnish enantiomerically pure penultimate intermediates (+)-**17a** (96 % ee) and *ent*-(−)-**17b** (94 % ee), respectively, in overall 50% yield. Final, biphasic, transfer catalytic hydrogenolysis[31] of **17a** and **17b** served to quantitatively remove the benzyl ether and provided (+)-**3a** ($[\alpha]^{23}_D$ −1.73° (*c* 0.11, DMF))[32] and its enantiomer (−)-**3b** ($[\alpha]^{23}_D$ −2.1° (*c* 0.12, DMF)), respectively.

The biological activity, determined in an *in vitro* cytotoxicity assay,[33] showed that duocarmycin SA analogue, (+)-**3a** (GC3/C1; IC_{50} = 100 pM) was highly potent and in the same range as that of the natural product (+)-**1** (L1210; IC_{50} = 10 pM). Furthermore, the natural enantiomer (+)-**3a** displayed 7−50-fold higher potentcy than the unnatural isomer, *ent*-(−)-**3b** (Table 1), consistent with the biological findings of duocarmycin SA ((+)-**1**) and its enantiomer.[8a] These preliminary results are sufficiently encouraging to warrant further studies to fully characterize the biological properties of these agents and provided the incentive to develop the refined synthetic approach detailed herein.

Conclusion

A concise, total synthesis of seco-(+)- and *ent*-(−)-oxaduocarmycins has been achieved in 13 synthetic steps. Central to this strategy was an aryl radical cyclization onto a vinyl chloride, followed by a preparatively useful resolution procedure. The tactical improvement defined in this work shortens approaches to related agents[20] by 2−4 synthetic steps. This methodology should find application as a general synthetic approach to other members of this class of agents and related analogues.

Experimental Section

Ethyl 2-(6-Formyl-2-methoxy-4-nitrophenoxy)acetate (5). To a rapidly stirring solution of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde **4** (100 g, 0.507 mol) in dry methanol (1.5 L) was added powdered potassium hydroxide (85%, 37.1 g, 0.562 mol) and the mixture heated at reflux for 45 min. Methanol solvent was removed *in vacuo* and the resulting solid residue suspended in dimethylformamide (1.5 L). The mixture was cooled to 0 °C and ethyl bromoacetate (103 mL, 0.925 mol) added. The solution was warmed to room temperature and stirred for 36 h. The solvent was removed *in vacuo* and the resulting solid residue was diluted with water (3 L) and extracted with ethyl acetate (8 × 1 L). The combined organic extracts were washed with water (1 L) and brine (1 L), dried (Na_2SO_4), and concentrated to give the desired product **5** (136.5 g, 95%) as a tan solid: mp 109−110 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.48 (s, 1H), 8.09 (d, J = 2.94 Hz, 1H), 8.06 (d, J = 2.57 Hz, 1H), 5.06 (s, 2H), 4.14 (q, J = 6.99 Hz, 2H), 4.00 (s, 3H), 1.19 (t, J = 6.99 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 188.4 (CH), 168.6 (C), 154.4 (C), 152.0 (C), 129.3 (C), 125.9 (C), 115.4 (CH), 111.6 (CH), 69.2 (CH_2), 61.6 (CH_2), 56.7 (CH_3), 14.1 (CH_3); IR (KBr) ν_{max} 3100, 3080, 3000, 2950, 2910, 1755, 1698, 1585, 1526, 1479, 1352, 1203, 1053, 744 cm^{-1}; UV (EtOH) λ_{max} 209 (ϵ = 10739), 245 (ϵ = 12353), 294.5 (ϵ = 5178) nm; FDMS *m/z* 284 (M^+, 100). Anal. Calcd for $C_{12}H_{13}NO_7$: C, 50.89; H, 4.63; N, 4.95. Found: C, 50.82; H, 4.50; N, 4.76.

Methyl 7-Methoxy-5-nitrobenzofuran-2-carboxylate (6). 1,8-Diazabicyclo[5.4.0]undec-7-ene (80 mL, 0.535 mol) was added to a solution of benzaldehyde **5** (136.4 g, 0.482 mol) in ethanol (2.5 L) and the solution heated at reflux for 4 h. The reaction mixture was cooled to room temperature and the precipitated solid filtered, washed with cold ethanol (600 mL), and dried (*in vacuo* at 40 °C) to provide benzofuran **6** (56.1 g, 44%) as a yellow solid: mp 161−162 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.38 (d, J = 1.84 Hz, 1H), 7.93 (s, 1H), 7.90 (d, J = 2.21 Hz, 1H), 4.40 (q, J = 6.99 Hz, 2H), 4.10 (s, 3H), 1.36 (t, J = 6.99 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 158.3 (C), 148.4 (C), 147.8 (C), 145.8 (C), 145.3 (C), 127.7 (C), 114.2 (CH), 111.3 (CH), 103.8 (CH), 61.9 (CH_2), 56.5 (CH_3), 14.2 (CH_3); IR (KBr) ν_{max} 3500, 3200, 3000, 2950, 1718, 1529, 1345, 1322, 1297, 1188, 1096, 979, 944, 882, 739 cm^{-1}; UV (EtOH) λ_{max} 213 (ϵ = 14538), 264.5 (ϵ = 28797) nm; FDMS *m/z* 265 (M^+, 100). Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.08; H, 4.10; N, 5.29.

7-Hydroxy-5-nitrobenzofuran-2-carboxylic Acid (7). Methoxybenzofuran **6** (55.9 g, 0.211 mol) was combined with pyridine hydrochloride (243 g, 2.11 mol) in a flask equipped with a paddle stirrer. The two solids were heated neat at 170 °C with vigorous stirring for 18 h. The mixture was allowed to cool to ~50 °C and then poured into ice−water (2 L). The precipitated solid was filtered and washed with water (1 L). The crude solid was dissolved in 1 N sodium hydroxide (1.5 L) and washed with ethyl acetate (2 × 500 mL). Concentrated hydrochloric acid was added to the aqueous solution until pH 3 was reached. The precipitated product was filtered, washed with water, and dried (*in vacuo* at 50 °C) to give phenol **7** (44 g, 88%) as a pale yellow solid: mp 189−191 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.93 (s, 1H), 11.41 (s, 1H), 8.21 (d, J = 2.21 Hz, 1H), 7.81 (s, 1H), 7.71 (d, J = 2.21 Hz, 1H); IR (KBr) ν_{max} 3274 (br), 3093, 2542, 1694, 1530, 1347, 1287, 1225, 1193, 791 cm^{-1}; UV (EtOH) λ_{max} 208 (ϵ = 15442), 263.5 (ϵ = 18538) nm; FDMS *m/z* 223 (M^+, 100). Anal. Calcd for $C_9H_5NO_6$: C, 48.44; H, 2.26; N, 6.28. Found: C, 48.74; H, 2.41; N, 6.28.

Methyl 7-Hydroxy-5-nitrobenzofuran-2-carboxylate (8). Acetyl chloride (13 mL, 186 mmol) was added dropwise to dry methanol (1.5 L) at 0 °C and the solution stirred at room temperature for 0.5 h. Carboxylic acid **7** (39.6 g, 177 mmol) was added to the acidic methanol and the mixture heated at reflux, under a nitrogen atmosphere, for 18 h. The reaction was cooled to room temperature and the resulting precipitate filtered, washed with cold methanol (500 mL), and dried to give methyl ester **8** (41.2 g, 98%) as a light tan solid: mp 151−152 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.48 (s, 1H), 8.23 (d, J = 2.21 Hz, 1H), 7.91 (s, 1H), 7.73 (s, 1H), 3.93 (s, 3H); IR (KBr) ν_{max} 3281, 1688, 1582, 1523, 1442, 1356, 1328, 1256, 1102, 969, 901, 810, 744 cm^{-1}; UV (EtOH) λ_{max} 213 (ϵ = 16556), 267.5 (ϵ = 26855) nm; FDMS *m/z* 238 (M^+, 100). Anal. Calcd for $C_{10}H_7NO_6$: C, 50.64; H, 2.97; N, 5.91. Found: C, 50.85; H, 3.01; N, 5.88.

Methyl 5-Amino-7-hydroxybenzofuran-2-carboxylate (9). To a solution of nitrobenzofuran **8** (42 g, 177 mmol) in tetrahydrofuran:methanol (1:1, 1.5 L) was added 5% palladium−Al_2O_3 (5 g) and the mixture stirred at room temperature under 60 psi hydrogen atmosphere for 4 h. The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give a solid, which was purified by flash chromatography (gradient: 0−5% methanol:dichloromethane) to provide aminobenzofuran **9** (35.6 g, 97%) as a tan solid: mp 201−202 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.93 (s, 1H), 7.44 (s, 1H), 6.29 (d, J = 2 Hz, 1H), 6.24 (d, J = 1.75 Hz, 1H), 4.92 (s, 2H), 3.85 (s, 3H); IR (KBr) ν_{max} 3416, 3335, 2947, 1713,

(30) Boger, D. L.; Machiya, K. *J. Am. Chem. Soc.* **1992**, *114*, 10056.
(31) (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.
(32) The absolute configuration at C1 in analogue (+)-**3a** was assigned based on analogy of the biological activity with (+)-DSA (**1**).
(33) Procedures are described in the experimental section. For T222 tumor cell line also see: ref 15; for CCRF−CEM and GC3/C1 tumor cell lines also see: Mosmann, T. *J. Immunol. Meth.* **1983**, *65*, 55−62.

1610, 1568, 1454, 1434, 1356, 1204, 1155 cm^{-1}; UV (EtOH) λ_{max} 235.5 (ϵ = 20635), 290.5 (ϵ = 15655) nm; FDMS *m/z* 207 (M^+, 100). Anal. Calcd for $C_{10}H_9NO_4$ requires: C, 57.97; H, 4.38; N, 6.76%. Found: C, 57.72; H, 4.28; N, 6.63%.

Methyl 5-(*N*-(*tert*-Butyloxycarbonyl)amino)-7-hydroxybenzofuran-2-carboxylate (10). To a solution of amine **9** (35.6 g, 172 mmol) in tetrahydrofuran (750 mL) was added di-*tert*-butyl dicarbonate (48 g, 222 mmol) and the mixture stirred at room temperature for 24 h. The solvent was removed *in-vacuo* and the residue dissolved in ethyl acetate (1.5 L), washed with 1 N aqueous hydrochloric acid (2 × 200 mL), water (2 × 600 mL), and brine (1 × 600 mL), and then dried (Na_2SO_4). The organic solution was passed through a pad of silica gel and concentrated *in vacuo* to furnish Boc amine **10** (49.4 g, 93%) as a white powder: mp 190−192 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.34 (s, 1H), 9.34 (s, 1H), 7.65 (s, 1H), 7.37 (d, J = 1.47 Hz, 1H), 7.10 (d, J = 1.84 Hz, 1H), 3.88 (s, 3H), 1.48 (s, 9H); IR (KBr) υ_{max} 3291, 1698, 1606, 1584, 1534, 1453, 1340, 1249, 1164, 1109, 1062, 976, 852, 763, 739 cm^{-1}; UV (EtOH) λ_{max} 211 (ϵ = 25983), 244.5 (ϵ = 31990), 287.5 (ϵ = 19236) nm; FDMS *m/z* 308 (M^+, 100). Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.88; H, 5.63; N, 4.60.

Methyl 5-(*N*-(*tert*-Butyloxycarbonyl)amino)-7-(benzyloxy)benzofuran-2-carboxylate (11). To a solution of phenol **10** (48.9 g, 159 mmol) in dichloromethane (1.5 L) were added benzyl alcohol (30 mL, 291 mmol) and triphenylphosphine (75.1 g, 286 mmol) at room temperture and under a dry nitrogen atmosphere. The solution was cooled to 0 °C and diethyl azodicarboxylate (DEAD) (50 g, 287 mmol) added dropwise. The reaction mixture was stirred at room temperature for 18 h and concentrated *in vacuo* and the solid residue purified by flash chromatoghaphy (gradient: 5−20% ethyl acetate/hexanes) to provide benzyl ether **11** (57 g, 90%) as a white solid: mp 141−143 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.43 (s, 1H), 7.71 (s, 1H), 7.55 (s, 2H), 7.53 (d, J = 1.75 Hz, 1H), 7.51−7.39 (m, 3H), 7.29 (d, J = 1.75 Hz, 1H), 5.22 (s, 2H), 3.87 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.6 (C), 152.9 (C), 146.0 (C), 144.6 (C), 142.1 (C), 136.1 (C), 135.2 (C), 128.6 (C), 128.5 (CH), 128.0 (CH), 127.6 (CH), 114.2 (CH), 104.3 (CH), 103.7 (CH), 80.5 (C), 71.0 (CH_2), 52.1 (CH_3), 28.3 (3 x CH_3); IR (KBr) υ_{max} 3440, 2982, 2954, 2934, 1725, 1606, 1582, 1528, 1320, 1158 cm^{-1}; UV (EtOH) λ_{max} 242 (ϵ = 29172), 280 (ϵ = 16141) nm; FDMS *m/z* 397 (M^+, 100). Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.48; H, 5.83; N, 3.52. Found: C, 66.25; H, 5.86; N, 3.69.

Methyl 5-(*N*-(*tert*-Butyloxycarbonyl)amino)-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate (12). A solution of benzofuran **11** (30 g, 75.5 mmol) in dry tetrahydrofuran (250 mL) was cooled to −60 °C and two drops of concentrated sulfuric acid, followed by *N*-bromosuccinamide (14.8 g, 83 mmol), added under a stream of dry nitrogen. The mixture was warmed to 0 °C over a period of 3 h and was then quenched with 0.1 N aqueous sodium bisulfite (5 mL). The organic solvent was removed *in vacuo* and the residue diluted with ethyl acetate (300 mL), washed with water (2 × 150 mL), and brine (2 × 150 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford aryl bromide **12** (34.3 g, 95%) as a light yellow solid: mp 140−142 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07 (s, 1H), 7.54−7.49 (m, 3H), 7.42−7.34 (m, 3H), 6.94 (s, 1H), 5.31 (s, 2H), 3.97 (s, 3H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.2 (C), 152.5 (C), 146.0 (C), 144.2 (C), 141.2 (C),135.8 (C),133.2 (C), 129.1 (C), 128.4 (CH), 128.2 (CH), 128.0 (CH), 114.0 (CH), 104.6 (CH), 94.2 (C), 81.1 (C), 71.2 (CH_2), 52.3 (CH_3), 28.2 (3 × CH_3); IR (KBr) υ_{max} 3700, 3440, 3000, 2983, 17231453, 1233, 1157 cm^{-1}; UV (EtOH) λ_{max} 212.5 (ϵ = 27223), 246 (ϵ = 28581), 287 (ϵ = 14281) nm; FDMS *m/z* 475 (M^+, 100). Anal. Calcd for $C_{22}H_{22}NO_6Br$: C, 55.48; H, 4.65; N, 2.94; Br, 16.78%. Found: C, 55.20; H, 4.70; N, 3.20; Br, 16.50.

Methyl 5-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)amino]-7-(benzyloxy)-4-bromobenzofuran-2-carboxylate (13). Boc amine **12** (1.43 g, 3 mmol) was added portionwise to a suspension of sodium hydride (60% in mineral oil; 156 mg, 3.90 mmol) in dry dimethylformamide (8.0 mL) at room temperature and under nitrogen. The resulting dark yellow mixture was stirred at room temperature for 40 min and cooled to 0 °C and then neat (*E*:*Z*)-1,3-dichloropropene (846 μL, 9 mmol) added. The reaction was allowed to warm to room temperature, stirred for a further 15 h, quenched with brine (4 mL), and extracted with ethyl acetate (3 × 150 mL). Combined, dried ($MgSO_4$) organics were concentrated *in vacuo*, and the resulting crude brown oil was purified by flash chromatography (gradient: 0−20% ethyl acetate/hexanes) to give vinyl chloride **13** (1.36 g, 82%) as a low melting yellow glass: (*E*:*Z* vinyl chlorides and NBoc rotomers): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (s, 1H), 7.48−7.20 (m, 5H), 6.85−6.71 (m, 1H), 5.99−5.85 (m, 2H), 5.32 (br s, 2H), 4.46 (dd, J = 15.5 and 6.2 Hz, 1H), 4.35−4.20 (m, 1H), 3.98 (s, 3H), 1.5 (br s, 3H), 1.28 (br s, 6H);^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.1 (C), 153.8 (C), 146.4 (C), 146.3 (C), 135.8 (C), 135.7 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.0 (CH), 120.7 (CH), 114.8 (CH), 114.7 (C), 113.3 (CH), 80.6 (C), 71.4 (CH_2), 71.3 (CH_2), 52.4 (CH_3), 28.0 (CH_3); IR ($CHCl_3$) υ_{max} 2981, 1729,1 698, 1368, 1165 cm^{-1}; UV (EtOH) λ_{max} 203 (ϵ = 32586), 245.5 (ϵ = 30885), 286.5 (ϵ = 17684) nm; FDMS *m/z* 551 (M^+, 100). Anal. Calcd for $C_{25}H_{25}NO_6Cl$ Br: C, 54.51; H, 4.57; N, 2.58; Cl, 6.44; Br, 14.51; Found: C, 54.31; H, 4.60; N, 2.68; Cl, 6.72; Br, 14.42.

Methyl (1*R*/*S*)-5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-furano[3,2-*e*]indole-7-carboxylate (14). To a solution of aryl bromide **13** (12.30 g, 22.34 mmol) in dry benzene (1.49 L) were added tri-*n*-butyltin hydride (6.52 mL, 24.57 mmol) and catalytic 2,2′-azobis(isobutyronitrile) (AIBN) (183 mg, 1.12 mmol). The solution was deoxygenated by bubbling dry nitrogen through the solution at room temperature for ~1 h. The reaction mixture was then heated at reflux for 3.5 h and concentrated *in vacuo* to give an oily residue. Trituation of the crude oil with hexanes provided a solid which was filtered and washed with hexanes (3 × 500 mL) to give indoline **14** (7.79 g, 72%) as an off-white solid: mp 137−139 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (br s, 1H), 7.54−7.30 (m, 6H), 5.28 (s, 2H), 4.17 (apparent t, J = 10.4 Hz, 1H), 4.08−3.98 (m, 1H), 3.95 (s, 3H), 3.91−3.71 (m, 2H), 3.56 (apparent t, J = 10.3 Hz,1H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.4 (C), 152.2 (C), 146.5 (C), 144.9 (C), 142.3 (C), 136 1 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 111.6 (CH), 100.1 (C), 70.9 (CH_2), 52.9 (CH_2), 52.2 (CH_3), 46.6 (CH_3), 41.5 (C), 28.4 (3 × CH_3); IR ($CHCl_3$) υ_{max} 2956, 1725, 1695, 1497, 1158 cm^{-1}; UV (EtOH) λ_{max} 219 (ϵ = 27621), 254.5 (ϵ = 38111), 285 (ϵ = 14659), 346 (ϵ = 2729) nm; FDMS *m/z* 471 (M^+, 100). Anal. Calcd for $C_{25}H_{26}NO_6Cl$; C, 63.63; H, 5.55; N, 2.97; Cl, 7.51; Found: C, 63.35; H, 5.51; N, 2.74; Cl, 7.30.

Resolution of 14. Twenty micron Chiralpak AD (Amylose) (600 g) was slurried in 1-propanol (1200 mL) and transferred to a 8 cm Prochrom column and the bed compressed at a pressure of 85 Bar resulting in a 8 cm × 24 cm configuration with a column volume (CV) of 964 mL. Preparative separations were preformed at a flow rate of 225 mL/min with a column pressure of 11 Bar. Racemate **14** (360 mg) was dissolved in eluent 1-propanol/hexanes (51:49, 300 mL) and charged on the column using a sample pump. Chromatograms from a run on the Prochrom column is illustrated in Figure 1. Racemate **14** (10.57 g) was resolved, in 35 runs on the 8 cm column, with an optimized time of 13 min per run and effluent monitored at 280 nm, to give:

Methyl (1*S*)-5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-furano[3,2-*e*]indole-7-carboxylate (14a). First peak (t_R = 5.6 min, 97.6 % ee, 5.16 g, 49 % recovery), as a white solid: $[\alpha]^{23}_D$ −10.8 ° (*c* 0.5, $CHCl_3$). Mp 130−132 °C dec; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (br s, 1H), 7.55−7.33 (m, 6H), 5.29 (s, 2H), 4.18 (apparent dd, J = 11.3 and 10 Hz, 1H), 4.08−3.93 (m, 1H), 3.96 (s, 3H), 3.87−3.80 (m, 2Hl), 3.60 (apparent t, J = 10.4 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.4 (C), 152.2 (C), 146.5 (C), 144.9 (C), 142.3 (C), 136 1 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 111.6 (CH), 100.1 (C), 70.9 (CH_2), 52.9 (CH_2), 52.2 (CH_3), 46.6 (CH_3), 41.5 (C), 28.4 (3 × CH_3); IR (KBr) υ_{max} 2990, 1737, 1696, 1152, 1137, 767, 696 cm^{-1}; UV (EtOH) λ_{max} 219 (ϵ = 27870), 254.5 (ϵ = 39132), 284.5 (ϵ = 14997), 346 (ϵ = 2901) nm; FDMS *m/z* 470.9 (M^+, 100). Anal. Calcd for $C_{25}H_{26}NO_6$-

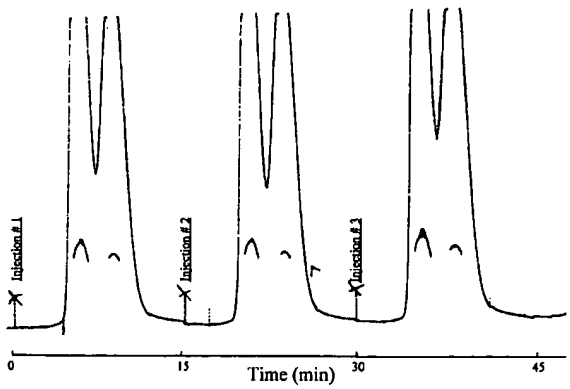

Figure 1. Typical chromatograms of the separation of racemate **14** on a Chiralpak AD (Amylose) column.

Cl: C, 63.63; H, 5.55; N, 2.97; Cl, 7.51; Found: C, 63.56; H, 5.53; N, 2.67; Cl, 7.72.

Methyl (1*R*)-5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-furano[3,2-*e*]indole-7-carboxylate (14b). Second peak (t_R = 7.4 min, 95.5 % ee, 5.04 g, 48 % recovery) as a white solid: $[\alpha]^{23}_D$ +11.2° (*c* 0.5, $CHCl_3$). mp 131−133 °C dec; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (br s, 1H), 7.55−7.28 (m, 6H), 5.29 (s, 2H), 4.18 (dd, *J* = 11.6 and 10 Hz,1H), 4.08−3.98 (m, 1H), 3.96 (s, 3H), 3.88−3.80 (m, 2Hl), 3.60 (apparent t, *J* = 10.4 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.4 (C), 152.2 (C), 146.5 (C), 144.9 (C), 142.3 (C), 136 1 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 111.6 (CH), 100.1 (C), 70.9 (CH_2), 52.9 (CH_2), 52.2 (CH_3), 46.6 (CH_3), 41.5 (C), 28.4 (3 × CH_3); IR (KBr) υ_{max} 2990, 1736, 1697, 1499, 1424, 1349, 1208, 1152, 1137, 762, 697 cm^{-1}; UV (EtOH) λ_{max} 219.5 (ϵ = 26377), 254.5 (ϵ = 37628), 284.5 (ϵ = 14440), 346.5 (ϵ = 2823) nm; FDMS *m/z* 470.9 (M$^+$, 100). Anal. Calcd for $C_{25}H_{26}NO_6Cl$: C, 63.63; H, 5.55; N, 2.97; Cl, 7.51; Found: C, 63.91; H, 5.58; N, 3.13; Cl, 7.59.

Methyl (1*S*)-5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3*H*-furano[3,2-*e*]indole-7-carboxylate (15a). Boc indoline **14a** (800 mg, 1.697 mmol) was added to a dry solution of 4 N HCl in dioxane (25 mL) at 0 °C and under nitrogen. The solution was stirred at 0 °C for 8 h and the solvent removed at 0 °C under high vacuum to provide amine hydrochloride salt **15a** (690mg, 100%) as an unstable brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07 (s, 1H), 7.55−7.52 (m, 2H), 7.47−7.39 (m, 3H), 7.13 (s, 1H), 5.32 (s, 2H), 4.14−3.91 (m, 2H), 3.91 (s, 3H), 3.73−3.60 (m, 2H), 3.51−3.47 (m, 1H); IR (KBr) υ_{max} 3400 (br), 1717, 1584, 1333, 1317, 1207, 1141, 1104, 915, 727 cm^{-1}; UV (EtOH) λ_{max} 243 (ϵ = 18536), 285 (ϵ = 12985), 359 (ϵ = 2272), 389 (ϵ = 1674) nm; FDMS *m/z* 371 (Free amine, M$^+$, 100). Anal. Calcd for $C_{20}H_{19}NO_4Cl_2$: C, 58.84; H, 4.69; N, 3.43; Cl, 17.37. Found: C, 58.71; H, 4.85; N, 3.13; Cl, 16.82.

Methyl (1*R*)-5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3*H*-furano[3,2-*e*]indole-7-carboxylate (15b). Boc indoline **14b** (1.00g, 2.12 mmol) was added to a dry solution of 4 N HCl in dioxane (28 mL) at 0 °C and under nitrogen. The solution was stirred at 0 °C for 8 h and the solvent removed at 0 °C under high vacuum to provide amine hydrochloride salt **15a** (865mg, 100%) as an unstable brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.08 (s, 1H), 7.55−7.52 (m, 2H), 7.47−7.39 (m, 3H), 7.15 (s, 1H), 5.32 (s, 2H), 4.14−3.91 (m, 2H), 3.91 (s, 3H), 3.72−3.61 (m, 2H), 3.51−3.48 (m, 1H); IR (KBr) υ_{max} 3400 (br), 1717, 1583, 1333, 1317, 1275, 1207, 1141, 1104, 728 cm^{-1}; UV (EtOH) λ_{max} 211 (ϵ = 26721), 243 (ϵ = 18796), 285 (ϵ = 13166), 359 (ϵ = 2189) nm; FDMS *m/z* 371 (Free amine, M$^+$, 100). Anal. Calcd for $C_{20}H_{19}NO_4Cl_2$: C, 58.84; H, 4.69; N, 3.43; Cl, 17.37. Found: C, 58.78; H, 4.72; N, 3.18; (Cl, 16.82).

Methyl (1*R*)-5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-3*H*-furano[3,2-*e*]indole-7-carboxylate (17a). To a dry solution of amine hydrochloride salt **15a** (173 mg, 0.424 mmol) in dimethylformamide (4.0 mL) was added sodium bicarbonate (178 mg, 2.12 mmol) followed by 5,6,7-trimethoxyindolecarboxylic acid **16** (128 mg, 0.509 mmol) and finally 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI) (244 mg, 1.272 mmol) and the mixture stirred at room temperature under nitrogen for 18 h. The solvent was reduced to ~1/2 the original volume and ethyl acetate (20 mL) added. The organics were washed with 0.1 N aqueous hydrochloric acid (2 × 10 mL), water (10 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL) and then dried ($MgSO_4$). Concentration of the organics followed by purification of the resulting crude solid by flash chromatography (gradient: 10−40% ethyl acetate/hexanes) provided amide **17a** (127 mg, 50%, HPLC (analytical ChiraCel OD column; flow rate = 1.0 mL/min; UV detection at λ = 254 nm; eluent, CH_3CN:H_2O 90:10): t_R = 11.08 min; 96 % ee) as a white powder: $[\alpha]^{23}_D$ +13.6° (*c* 0.5, $CHCl_3$). mp 182−183.5 °C (EtOAc/hexanes, white needles); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (brs, 1H), 8.31 (s, 1H), 7.56−7.52 (m, 3H), 7.43−7.28 (m, 3H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.87 (s, 1H), 5.35 (s, 2H), 4.71 (apparent t, *J* = 10 Hz, 1H), 4.59 (dd, *J* = 10.9 and 4.0 Hz, 1H), 4.08 (s, 3H), 4.07−3.88 (m, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.61 (dd, *J* = 11 and 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.9 (C), 159.3 (C), 150.1 (C), 146.7 (C), 144.7 (C), 143.1 (C), 141.0 (C), 140.5 (C), 138.8 (C), 136.0 (C), 129.6 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 125.4 (C), 123.9 (C), 123.5 (C), 114.7 (C), 111.5 (CH), 106.4 (CH), 102.4 (CH), 97.6 (CH), 70.9 (CH_2), 61.4 (CH_3), 61.0 (CH_3), 56.2 (CH_3), 55.0 (CH_2), 52.3 (CH_3), 46.3 (CH_2), 43.0 (CH); IR (KBr) υ_{max} 3459, 2936, 1732, 1622, 1494, 1308, 1203, 744, 697 cm^{-1}; UV (EtOH) λ_{max} 208.5 (ϵ = 35611), 297 (ϵ = 22216), 326 (ϵ = 24475) nm; FDMS *m/z* 604 (M$^+$, 100). Anal. Calcd for $C_{32}H_{29}N_2O_8Cl$: C, 63.52; H, 4.83; N, 4.63; Cl, 5.86. Found: C, 63.58; H, 4.87; N, 4.39; Cl, 6.02.

(−)-(1*R*)-Methyl 5-(Benzyloxy)-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-3*H*-furano[3,2-*e*]indole-7-carboxylate (17b). Amine **15b** (216 mg, 0.530 mmol) was coupled to 5,6,7-trimethoxyindolecarboxylic acid **16**, in the same manner described above, to furnish amide **17b** (161 mg, 50%, HPLC (analytical ChiraCel OD column; flow rate = 1.0 mL/min; UV detection at λ = 254 nm; eluent, CH_3CN:H_2O 90:10): **17b**:: t_R = 8.42 min; 94 % ee) as a white solid: $[\alpha]^{23}_D$ −13.2° (*c* 0.5, $CHCl_3$); mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.41 (brs, 1H), 8.31 (s, 1H), 7.55−7.51 (m, 3H), 7.43−7.33 (m, 3H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.86 (s, 1H), 5.35 (s, 2H), 4.70 (apparent t, *J* = 9.9 Hz, 1H), 4.58 (dd, *J* = 10.9 and 3.9 Hz, 1H), 4.08 (s, 3H), 4.04−3.88 (m, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.60 (dd, *J* = 10.8 and 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 159.9 (C), 159.3 (C), 150.1 (C), 146.7 (C), 144.7 (C), 143.1 (C), 141.0 (C), 140.5 (C), 138.8 (C), 136.0 (C), 129.6 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 125.4 (C), 123.9 (C), 123.5 (C), 114.7 (C), 111.5 (CH), 106.4 (CH), 102.4 (CH), 97.6 (CH), 70.9 (CH_2), 61.4 (CH_3), 61.0 (CH_3), 56.2 (CH_3), 55.0 (CH_2), 52.3 (CH_3), 46.3 (CH_2), 43.0 (CH); IR (KBr) υ_{max} 2937, 1731, 1622, 1494, 1416, 1309, 1204, 1109, 744, 697 cm^{-1}; UV (EtOH) λ_{max} 209 (ϵ = 44076), 297.5 (ϵ = 26058), 326 (ϵ = 30391) nm; FDMS *m/z* 603.7 (M$^+$, 100). Anal. Calcd for $C_{32}H_{29}N_2O_8Cl$: C, 63.53; H, 4.83; N, 4.63; Cl, 5.86. Found: C, 63.74; H, 4.81; N, 4.40; Cl, 6.01.

Methyl (1*S*)-5-hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-3*H*-furano-[3,2-*e*]indole-7-carboxylate (3a). To a solution of benzyl ether **17a** (149 mg, 0.247 mmol) in tetrahydrofuran (5.80 mL) was added 10% aqueous ammonium formate (560 μL). The solution was cooled to 0 °C and 10% Pd−C (56 mg) added. The reaction mixture was stirred for 5 h, filtered through a pad of Celite, and concentrated to provide (+)-oxaduocarmycin SA (**3a**) (122 mg, 96%) as a yellow powder: $[\alpha]^{23}_D$ +1.73° (*c* 0.11, DMF); mp 265−268 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.39 (d, *J* = 1.14 Hz, 1H), 10.52 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.92 (s, 1H), 4.66 (apparent t, *J* = 10 Hz, 1H), 4.34 (dd, *J* = 10.6 and 3.54 Hz, 1H), 4.08−4.02 (m,1H), 3.98−3.94 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.34−3.26 (buried m, 1H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 160.0 (C), 159.1 (C), 149.2 (C), 145.6 (C), 142.6 (C), 141.9 (C), 140.9 (C), 139.9 (C), 139.1 (C), 131.0 (C), 125.3 (C), 124.2 (C), 123.2 (C), 114.3 (C), 113.0 (CH), 106.0 (CH), 104.0 (CH), 98.1 (CH), 61.1 (CH_3), 61.0 (CH_3), 56.0 (CH_3), 54.8 (CH_2) 52.3 (CH_3), 47.4 (CH_2), 41.4 (CH); IR (KBr) υ_{max} 3449,

1726, 1589, 1492, 1453, 1310, 1198, 1106 cm^{-1}; UV (EtOH) λ_{max} 304 (ϵ = 8970), 328 (ϵ = 9326) nm; FDMS *m/z* 514 (M^+, 100). Anal. Calcd for $C_{25}H_{23}N_2O_8Cl$: C, 58.31; H, 4.50; N, 5.44; Cl, 6.89. Found: C, 58.25; H, 4.66; N, 5.29; Cl, 6.61.

Methyl (1*R*)-5-Hydroxy-1-(chloromethyl)-1,2-dihydro-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-3*H*-furano-[3,2-*e*]indole-7-carboxylate (3b). Benzyl ether **17b** (130 mg, 0.215 mmol) was deprotected, in the same manner described previously, to give (−)-oxaduocarmycin SA (**3b**) (109 mg, 99%) as a yellow solid: $[\alpha]^{23}_D$ −2.1° (*c* 0.12, DMF); mp 264−267 °C; ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 10.51 (s, 1H), 7.96 (s, 1H), 7.94 (s, 1H), 6.98 (d, J = 1.7 Hz, 1H), 6.92 (s, 1H), 4.67 (apparent t, J = 10 Hz, 1H), 4.32 (dd, J = 11.4 and 4.2 Hz, 1H), 4.08−4.05 (m, 1H), 3.98−3.92 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.36−3.27 (buried m, 1H); ^{13}C NMR (DMSO-d_6, 63 MHz) δ 160.0 (C), 159.1 (C), 149.2 (C), 145.6 (C), 142.6 (C),141.9 (C), 140.9 (C), 139.9 (C), 139.1 (C), 131.0 (C), 125.3 (C), 124.2 (C), 123.2 (C), 114.3 (C), 113.0 (CH), 106.0 (CH), 104.0 (CH), 98.1 (CH), 61.1 (CH_3), 61.0 (CH_3), 56.0 (CH_3), 54.8 (CH_2) 52.3 (CH_3), 47.4 (CH_2), 41.4 (CH); IR (KBr) υ_{max} 3450, 1725, 1586, 1492, 1429, 1310, 1107, 746 cm^{-1}; UV (EtOH-sparingly soluble) λ_{max} 208, 303, 328 nm; FDMS *m/z* 514 (M^+, 100). Anal. Calcd for $C_{25}H_{23}N_2O_8Cl$: C, 58.31; H, 4.50; N, 5.44; Cl, 6.89. Found: C, 58.55; H, 4.67; N, 5.14; Cl, 6.92.

***In Vitro* Cytotoxicity Assays.** T222 (human lung epidermoid carcinoma)[14] cells (1×10^4) were distributed in each well of 96 well tissue culture plates and incubated in leucine-deficient media (leucine-free DMEM, 13 μg/mL L-leucine, 29.9 μg/mL L-glutamine, 50 μg/mL gentamicin, and 10% dialyzed fetal bovine serum) for 16 h at 37 °C in 5% carbon dioxide/air atmosphere. The medium was removed aseptically and compound dilutions added in leucine-deficient medium (200 μL). After 48 h the media was removed and 4 μCi (^{3}H-Leucine-NEN, Boston, MA) was added to each well. The plates were returned to the incubator for 24 h. Radioactivity incorporated into macromolecules was determined using an automated cell harvester and liquid scintillation techniques. Data were evaluated as % reduction in incorporation of radioactivity relative to controls incubated in medium without compound to yield a 50% cytotoxic concentration (IC_{50}).

A modification of the original MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimeteric assay, described by Mosmann[33] that measures the reduction of MTT to a violet-colored formazan by living cells, was used for the CCRF−CEM and GC3/C1 cell assays. The tumor cells (1×10^4) were seeded in assay medium (100 μL)/well in 96-well flat bottom tissue culture plates (Costar, Cambridge, MA). Assay medium consisted of RPMI-1640 medium supplemented with 10% dialyzed fetal bovine serum. Well 1A was left blank (100 μL of growth medium without cells). Stock solutions of test compounds were prepared in DMSO at 1 mg/mL, and a series of 2-fold dilutions were made in Dulbecco's phosphate-buffered saline (PBS). Aliquots (10 μL) of each concentration were added to triplicate wells. The compounds were tested at concentrations ranging from 0.01 to 0.00008 μg/mL. Plates were incubated for 72 h at 37 °C in a humidified atmosphere of 5% CO_2-in-air. MTT was dissolved in PBS at 5 mg/mL, and following incubation of plates, a stock solution of MTT (10 μL) was added to the assay wells and the plates were incubated at 37 °C for an additional 2 h. DMSO (100 μL) was added to each well to thoroughly solubilize the formazan, and the plates were then read on a Dynatech (Alexandria, VA) MR600 reader using a test wavelength of 570 nm and a reference wavelength of 630 nm. The IC_{50} was determined as the concentration of drug required to inhibit cell growth by 50%.

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